REMARKS

Reconsideration is requested.

Claims 1-12 have been canceled, without prejudice.

Claims 13-29 have been added. No new matter has been added. Support for the newly added claims may be found throughout the specification and originally-filed claims.

Attached is a Rule 181 Petition for the Commissioner to invoke his supervisory authority and have the restriction requirement withdrawn, at least insofar as a single primer set and single probe are required to be elected. Consideration and a decision on the attached Petition is requested prior to issuance of a further Action on the merits by the Examiner so that the issues raised in the attached Petition may be considered by the Commissioner and the applicants may have a decision on the same prior to further consideration of the issues raised by the Examiner and so that the Examiner may consider any further issues raised by the Commissioner prior to the issuance of a further Action.

The Information Disclosure Statement filed March 13, 2001, which lists, among other things, document DE 197 16 456, is submitted to have been filed in compliance with the Rules. Specifically, the cited document was listed in the International Search Report from PCT/EP99/07065 and the relevance of the same is indicated as category "P" and "X". The International Search Report was filed with the Information Disclosure Statement and previously indicated as having been received by the Patent Office in the Notification of Acceptance dated September 14, 2001. A translation into the English

language of the document should not be required. The Examiner is requested to appreciate in this regard that page 600-119 of the August 2001, copy of the MPEP indicates that "the Examiner will consider the documents cited in the International Search Report in a PCT National Stage application when the Form PCT/DO/EO/903 indicates that both the International Search Report and the copies of the documents are present in the National Stage file". Form PCT/DO/EO/903 is the Notification of Acceptance referred to above.

The Examiner is also requested to see page 600-122 of the August 2001 version of the MPEP which indicates as follows:

> "Where the information listed [in a PTO-1449 Form] is not in the English language, but was cited in a Search Report or other action by foreign patent office in a counterpart foreign application, the requirement for a concise explanation of relevance can be satisfied by an English language version of the Search Report or Action which indicates the degree of relevance found by the foreign office. This may be an explanation of which portion of the reference is particularly relevant, to which claims it applies, or merely an "X", "Y", or "A" indication on a Search Report."

Accordingly, nothing further should be required. For completeness however attached is an English language translation of the cited DE 197 16 456. Return of an initialed copy of the previously submitted PTO-1449 Form, indicating consideration of the listed document, or return of a PTO 892 Form listing the same, is requested.

The objections to claims 3 and 4 noted on page 4 of Paper No. 11 are moot in view of the above. The claims have been rewritten with the Examiner's objections in mind.

The Section 112, second paragraph, rejection of claims 1-5 noted on pages 5-6 of Paper 11 are moot in view of the above. The newly submitted claims are believed to be definite.

The Examiner is urged to appreciate in this regard that claim 14, which is similar to canceled claim 2, refers to a gene region of *M. pneumoniae* and *C. pneumoniae* which is the spacer region between the 16S and the 23S rRNA sequences. Concerning the 16S-23S spacer region, also known by an ordinarily skilled person as the ITS (Internal Transcribed Spacer) region, one of ordinary skill in the art will appreciate the region consists of the transcribed nucleic acid sequence located between the 16S rRNA gene and the 23S rRNA gene. With regard to the alleged missing step, the applicants believe that the addition of a further step may unduly limit the scope of protection provided and should not be necessary as the disclosed method for detection comprises an amplification step which implicitly includes a detection. Such a detection may be achieved by using probes or other means known to those of ordinary skill in the art, such as, sequencing, restriction digest methods, et cetera.

The Section 103 rejection of claims 1-5 over Jannes, et al. (U.S. Patent No. 6,025,132), Claas (Journal of Virological Methods, 1992; 39 (1-2) 1013, abstract only), Paton (Journal of Clinical Microbiology, 1992; 30(4): 901-904, abstract only), Kinchington (Investigative Ophthalmology and Visual Science, 1994; 35(12): 4126-34, abstract only), Saikku (Clinical Microbiology and Infection, 1997; 3(6); 599-606), Gilbert

(Journal of Clinical Microbiology, 1996; 34(1): 140-143), Fluitt (WO 95/13396, May, 1995; Genenbl GE Assession No.: A4457), Jannes (WO 96/00298, January, 1996; Genenbl Assession No. A47982) and Echevarria (Journal of Clinical Microbiology, May, 1998; 36(5): 1388-1391), is moot in view of the above.

The claims are submitted to be patentable over the cited art. Consideration of the following in this regard is requested.

Initially, the applicants note the Examiner has required a combination of nine references to allege that the method, apparently limited to only one primer set and one probe, wherein one of the primers (i.e., SEQ ID NO. 19) has been indicated as not being taught or suggested by the art (see, page 10 of Paper No. 11), was obvious. The Examiner's consideration and interpretation of the art has been made, with due respect, with an impermissible use of hindsight.

Consideration of the following in this regard is requested.

It is curious that the Examiner has described at page 7 of Paper No. 11 that the claims are drawn to a method for detecting acute respiratory tract infection and a sample by simultaneous amplification of specific genes of various bacteria and viruses and yet the Examiner has not allowed for search and examination of more than one primer set or probe. The Examiner's comments in this regard emphasize the applicants belief that the restriction requirement is inappropriate.

The Examiner acknowledges that Saikku does not teach simultaneous amplification of all the nucleic acids from the pathogens that might be present in a sample or specific primers and probes to the specific regions claimed. See, page 7 of Paper No. 11. The Examiner has therefore attempted to combine the teachings of

documents relating to RT-PCR with a list of organisms that are suspected of being responsible for respiratory tract infections to allege the obviousness of the presently claimed invention. Motivation for such a combination is not found in the cited art.

Initially, the applicants note that Saikku is not believed to teach "that nucleic acid detection methods to diagnose respiratory diseases provides sensitive and specific diagnoses within twenty-four hours", as alleged by the Examiner at page 7 of Paper No. 11. The Examiner relies on the last paragraph before the "treatment" section on page 602 of Saikku. The applications however believe this passage reads as follows:

"Nucleic acid (NA) detection seems to be the diagnostic method of the future (...).", "(...) diagnostic companies are developing kits based on NA amplification for *Legionella spp*, *M. pneumoniae* and *Chlamydia pneumoniae*.") (emphasis added).

The applications believe that from this paragraph, it is very clear that, the author, who is believed to at least be of ordinary skill in the art, considers the nucleic acid detection method as a technology of the future. Such a teaching, at best, suggests that it may have been obvious-to-try to make the presently claimed method. Obvious-to-try however is not sufficient to establish *prima facie* obviousness.

Although the author mentions in his Table 1 many pathogens responsible for the respiratory tract infections, still, he explicitly limits his study and examples to 3 bacteria, using future tense to describe the technology for detecting these 3 bacteria.

Moreover, the Examiner acknowledges that "Saikku et al. does not teach simultaneous amplification of al of the nucleic acids from the pathogens that might be present in a sample or specific primers and probes to the specific regions claimed".

Therefore this publication cannot be used as an incentive for the skilled person to carry out a method for the simultaneous detection of up to 11 different pathogens.

Concerning Gilbert et al., as already explained in the description of the present patent application, the method used requires different assay conditions: for RSV one protocol is carried out, for PIV or picornaviruses another protocol is carried out (see page 141, first column, "for RSV, (...) combined annealing-extension at 70 C for 2 min"; "for PIV and picornaviruses (...) annealing at 55 C for 1 min, and extension at 70 C for 1 min").

Moreover the applicants believe the Examiner's assertion that "Gilbert et al. teaches simultaneous amplification" is an incorrect interpretation of the document.

It is correct that the term "simultaneous" is used many times in the publication but always associated with "infections". Indeed, the authors wanted to show that there are different organisms involved in the infection. But the way they have chosen, using a different protocols for different pathogens, could not motivate the skilled person to go further, making the method too complicated and too long to be carried out.

They did, themselves, raise the problem of how time consuming is their method which "may take up to several days" and of the costs-effectiveness (see page 142, 2nd column, first paragraph). And once again, while mentioning several organisms responsible for the respiratory tract infections, they have limited their study to 3 pathogens.

This latter characteristics is common to all of the publications cited by the Examiner. None of these documents could propose an amplification method for the

detection of more than 3 different organisms simultaneously, as is provided by the presently claimed invention.

It is clear to the applicants that the skilled person, with so many publications, all of them leading him in the same direction of a limitation of the number of organisms to be detected (1 to 3 maximum), in an inefficient and time-consuming method, would not reach the presently claimed invention.

The claims are submitted patentable over the cited art.

Grant of the attached Rule 181 Petition and a Notice of Allowance are requested.

Respectfully submitted,

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Method for detecting microorganisms, in particular those causing infectious diseases

Method for detecting microorganisms, in particular those causing infectious diseases, by means of simultaneous amplification of a plurality of target sequences in a reaction vessel, in a so-called multiplex PCR method, by contacting a patient's sample with a primer solution consisting of a plurality of primers, initiating a polymerase chain reaction (PCR), where, for disease-causing microorganisms which have only one RNA, part of the patient's sample is subjected to a preceding reverse transcription, and then the PCR products are subjected to a digoxigenin labelling with probes chosen appropriate for the primers, and subsequently obtaining information about the presence of a microorganism belonging to the primer by capture probe analysis and/or photometric analysable change in the colour value of the sample.

Description

The invention relates to a method for detecting microorganisms, in particular those causing infectious diseases.

Microorganisms causing infectious diseases, in particular those of the human respiratory tract, may cause diseases with particularly severe courses especially in weakened patients (e.g. with cardiovascular disorders or with cancer). However, even "normal" coryzal illnesses are the commonest of all human illnesses. The loss of work and money caused thereby in the Federal Republic of Germany alone each year reaches astronomical figures. They are caused by various microorganisms which induce only a comparatively weak defence in the body, for which

reason such infections can occur repeatedly. At least some of these disease-causing microorganisms can now be treated with antibiotics, although it is unfortunately not at present known how these disease-causing microorganisms can be distinguished from one another solely on the basis of the patients' symptoms. The methods known to date for detecting microorganisms causing coryzal illnesses are extremely complicated, time-consuming and costly.

In the first place, the practicability of culturing is low because the result is available only after a long time, at least days, mostly weeks, and culturing is extremely elaborate and therefore cost-intensive and, last but not least, has low sensitivity; the average paediatric hospital stay is 3 to 5 days so that the patient has usually returned home when the disease-causing microorganism is detected. Culturing the disease-causing microorganisms is therefore useless for acute patient care.

Serology, which is also known and in which an increase in the antibodies against a disease-causing microorganism in the patient is investigated, is likewise conditional on a very long run-up time. It is necessary to compare two blood samples from the patient which have been taken at an interval of 3 to 4 weeks.

For care of the patient it is crucially important to employ the drug which is correct for the particular disease-causing microorganism or, where appropriate, no antibiotic at all. A further necessity in the hospital is that various isolation measures must be taken, depending on the microorganism which has infected the patients, such as, for example, the cohorting of patients with one microorganism in one room, who are then cared for only by one member of the nursing staff. It is therefore very important that the particular disease-causing microorganism is recognized quickly.

The object on which the invention is based is to provide a rapid method for detecting the microorganisms which come under consideration.

This is achieved according to the invention by the features of the main claim. The dependent claims represent advantageous embodiments of the invention.

It is possible with the aid of the described polymerase chain reaction (PCR) for the first time also to detect rapidly and reliably microorganisms which cause disease in the respiratory tract. In this case it is possible to amplify a plurality of target sequences in one reaction vessel simultaneouly (multiplex PCR). This makes it possible to undertake epidemiological investigations in order to find out which microorganisms cause respiratory tract diseases in which population, and how frequently, and to inform the treating physician within one working day of whether the patient will profit from treatment with a particular antibiotic or not. It was not possible in the past to make this decision appropriately because no objective aid to decision was available.

The diagnostic multiplex PCR used for this purpose makes it possible, by contrast, to make a rapid decision concerning the administration of antibiotics on the basis of the microorganisms found. For example, infectious diseases caused by mycoplasmas or chlamydias can be treated with a macrolide antibiotic, whereas there is as yet no therapy for disease-causing viruses. If no disease-causing microorganism is detected, a bacterium must be suspected as the cause, depending on the clinical findings, in which case treatment with a beta-lactam antibiotic (pneumococci, haemophilus) is necessary.

The problem which occurs in particular in the implementation, of combining different primers in a multiplex PCR, is solved by the primers detailed in the dependent claims.

In this connection, the chosen selection of at least one of the primers

- Chlamydia pneumoniae
CpnA 5'-TGA CAA CTG TAG AAA TAC AGC-3'
CpnB 5'-CGC CTC TCT CCT ATA AAT-3'; and
- Mycoplasma pneumoniae
MP1 5'-AAG GAC CTG CAA GGG TTC GT-3'
MP2 5'-CTC TAG CCA TTA CCT GCT AA-3'

provides an indicator of whether treatment is necessary with a macrolide antibiotic, and the total number of nine different primers CpnA,-B; MP1,-2; EV1,-2; RSV1,-2; InfA NS1, NS2; InfB NS1, NS2; Adh1,-2; PIV1 1,2; PIV3 1,3 covers all the usual coryzal illnesses, so that if there is a negative finding it can be concluded that the cause is bacterial.

Although finding only viral microorganisms affords no direct pointer to therapy, epidemiological investigations and appropriate cohorting with patients infected by the same virus become possible, and hospital-acquired infections can be avoided.

Further features and advantages of the invention are evident from the following description of a preferred sample preparation and the performance of the method with suitable primers and probes.

In a sample preparation initially used for the experiments, for example, 100 µl of nasopharyngeal discharge are diluted with 100 µl of 0.9% NaCl solution and extracted with 1 volume of phenol/chloroform/isoamyl alcohol in a composition of

25:24:1 in a final concentration of 0.1% SDS. After centrifugation in a bench centrifuge for 5 minutes, the upper aqueous phase is aspirated off, extracted with chloroform/isoamyl alcohol 24:1 and centrifuged for 2 min. The nucleic acids in the supernatant are precipitated with 2.5 volumes of ethanol at a final concentration of 0.3 M sodium acetate for 5 min at -70°C, and spun down for 20 min. The pellet is taken up in 15 µl of diethyl pyrocarbonate-treated double-distilled H_2O.

Then 5 µl of this undergoes reverse transcription in a 20 µl reaction mixture with 50 mM Tris-HCl (pH 8.3), 75 mM KCl, 3 mM $MgCl_2$, 10 mM DTT, in each case 1 mM dATP, dCTP, dTTP and dGTP (e.g. from Pharmacia), 0.2 µg/µl hexanucleotide mix (e.g. from Boehringer Mannheim), 20 U of RNAsin (e.g. Promega) and 10 U of Mu-MLV reverse transcriptase (e.g. Eurogentec) (final concentrations in each case) at 37°C for 60 min. After thermal inactivation of the enzyme at 90°C for 5 min, the 20 µl are employed in the multiplex PCR.

The polymerase chain reaction takes place in an 80 µl reaction mixture with 10 mM Tris-HCl (pH 8.3), 50 mM KCl, 1.5 mM $MgCl_2$, 0.001% gelatin, in each case 0.2 mM dATP, dCTP, and dGTP, 0.19 mM dTTP, 0.01 mM digoxigenin-11-dUTP (Boehringer Mannheim), 1 µM of each primer solution (see below) and 5 U of ampliTaq Gold polymerase (Perkin-Elmer).

The PCR reaction takes place in the thermoblock of a PCR thermocycler (PE 9600 Perkin Elmer) after an initial 10-minute denaturation at 94°C using a temperature profile with a total of 40 cycles each consisting of denaturation at 94°C for 30 sec, hybridization of the primers at 50°C and DNA synthesis at 72°C, and a final 7-minute incubation at 72°C.

A PCR ELISA (Boehringer) follows to differentiate the PCR products. The digoxogen-labelled amplicons are immobilized with the aid of specific biotin-labelled probes onto streptavidin-coated microtitre plates. The bound hybrid can be detected with an anti-dioxygenin-peroxidase conjugate and a colour substrate.

For this purpose, in each case 25 µl of denaturation solution (0.2N NaOH, 0.1% SDS) and 5 µl of a PCR product are placed in the wells of the streptavidin-coated microtitre plates. 9 wells are charged for each PCR product. Denaturation for 10 minutes is followed by addition of the 9 different hybridization solutions which are composed of the particular biotinylated probe (final concentration 7.5 pmol/ml; see below for sequences) and hybridization buffer (Boehringer Mannheim).

After shaking at 37°C for 1 hour, the plate is washed three to five times with washing solution, and 200 µl of an anti-dig-peroxidase conjugate is placed in each well. After shaking at 37°C for 30 min, washing is repeated and the colour substrate ABTS is pipetted into the wells, and after shaking at 37°C for 30 min the change in colour can be measured photometrically in an ELISA reader at 405 nm. A 490 nm reference filter is used. Thus, colour changes occur only in the wells in which, owing to the probes, PCR product and the anti-dig peroxidase adhere to streptavidin.

The appended list indicates the primers used and the probes suitable therefor which were used:

Primers used:

Enterovirus:- EV1 5'-ATT GTC ACC ATA AGC AGC CA-3'
EV2 5'-TCC TCC GGC CCC TGA ATG CG-3'

Mycoplasma pneumoniae: MP1 5'-AAG GAC CTG CAA GGG TTC GT-3'
MP2 5'-CTC TAG CCA TTA CCT GCT AA-3'

Influenzavirus type A: InfA NS1 5'-AAG GGC TTT CAC CGA AGA GG-3'
InfA NS2 5'-CCC ATT CTC ATT ACT GCT TC-3'

Influenzavirus type B: InfB NS1 5'-ATG GCC ATC GGA TCC TCA AC-3'
InfB NS2 5'-TGT CAG CTA TTA TGG AGC TG-3'

Adenovirus: Adh1 5'-GCC GAG AAG GGC GTG CGC AGG TA-3'
Adh2 5'-ATG ACT TTT GAG GTG GAT CCC ATG GA-3'

Chlamydia pneumoniae: CpnA 5'-TGA CAA CTG TAG AAA TAC AGC-3'
CpnB 5'-CGC CTC TCT CCT ATA AAT-3'

Parainfluenzavirus type 1:
PIV1 1 5'-CAC ATC CTT GAG TGA TTA AGT TTG ATG A-3'
PIV1 2 5'-ATT TCT GGA GAT GTC CCG TAG GAG AAC-3'

Parainfluenzavirus type 3:
PIV3 1 5'-TAG CAG TAT TGA AGT TGG CA-3'
PIV3 2 5'-AGA GGT CAA TAC CAA CAA CTA-3'

Respiratory Syncytial Virus (RSV):
RSV1 5'-TGT TAT AGG CAT ATC ATT GA-3'
RSV 2 5'-TTA ACC AGC AAA GTG TTA GA-3'

Probes (3'-end biotinylated):

Sonden (3'-Ende biotinyliert):

Enterovirus: EV3 5'-GAA ACA CGG ACA CCC AAA GTA-3'

Mycoplasma pneumoniae: MP3 5'-ACT CCT ACG GGA GGC AGC AGT A-3'

Influenzavirus type A: InfA3 5'-GTC CTC ATC GGA GGA CTT GAA TGGAATGAT-3'

Influenzavirus type B: InfB3 5'-GTC AAG AGC ACC GAT TAT CAC C-3'

Adenovirus: Adh 3: 5'- CTC GAT GAC GCC GCG GTG C-3'

Chlamydia pneumoniae: CpnC 5'-TCT TGC TAC CTT CTG TAC TAA C-3'

Parainfluenzavirus type 1: PIV1C 5'-TAC CTT CAT TAT CAA TTG GTA AGT CAA TAT ATG -3'

Parainfluenzavirus type 3: PIV3C 5'-AAA ATT CCA AAA GAG ACC GGC -3'

RSV: RSV3 5'-TAC ACC TGC ATT AAC ACT AA-3'

It would also be advantageous to arrange, with the method of reserve hybridization, immobilized probes in separate regions on a support material, onto which each PCR product would then be put only for the evaluation.

Patent claims

1. Method for detecting microorganisms, in particular those causing infectious diseases, characterized by
   - a simultaneous amplification of a plurality of target sequences in a reaction vessel, a so-called multiplex PCR, in which a patient's sample is contacted with a primer solution consisting of a plurality of primers, and a polymerase chain reaction (PCR) is initiated,
   - where, for disease-causing microorganisms having only one RNA, part of the patient's sample is subjected to a preceding reverse transcription,
   - and then the PCR products are subjected to a digoxigenin labelling with probes chosen appropriate for the primers,
   - and subsequently to obtain information about the presence of a microorganism belonging to the primer by capture probe analysis and/or photometric analysable change in the colour value of the sample.

2. Method for detecting microorganisms according to Claim 1, characterized in that a Mycoplasma pneumoniae MP1, MP2 and Chlamydia pneumoniae CpnA, CpnB are used as primers to identify macrolide antibiotic-sensitive microorganisms.

3. Method for detecting microorganisms according to either of the preceding claims, characterized in that an RSV primer (respiratory syncytial virus) RSV1, RSV2 is used.

4. Method for detecting microorganisms according to any of the preceding claims, characterized in that an enterovirus primer EV1, EV2 is used.

5. Method for detecting microorganisms according to any of the preceding claims, characterized in that influenza virus primers type A and type B InfA NS1, InfA NS2 and InfB NS1, InfB NS2 are used.

6. Method for detecting microorganisms according to any of the preceding claims, characterized in that an adenovirus primer Adh 1 5'-GCC GAG AAG GGC GTG CGC AGG TA-3', Adh2 5'-ATG ACT TTT GAG GTG GAT CCC ATG GA-3' is used.

7. Method for detecting microorganisms according to any of the preceding claims, characterized in that parainfluenza virus primers type 1 PIV1 1, PIV1 2 and type 3 PIV3 1, PIV3 2 are used.

8. Method for detecting all therapeutically relevant microorganisms of the respiratory tract, characterized in that the primers

Enterovirus: EV1 5'-ATT GTC ACC ATA AGC AGC CA-3'
EV2 5'-TCC TCC GGC CCC TGA ATG CG-3'

Mycoplasma pneumoniae: MP1 5'-AAG GAC CTG CAA GGG TTC GT-3'
MP2 5'-CTC TAG CCA TTA CCT GCT AA-3'

Influenzavirus type A: InfA NS1 5'-AAG GGC TTT CAC CGA AGA GG-3'
InfA NS2 5'-CCC ATT CTC ATT ACT GCT TC-3'

Influenzavirus type B: InfB NS1 5'-ATG GCC ATC GGA TCC TCA AC-3'
InfB NS2 5'-TGT CAG CTA TTA TGG AGC TG-3'

Adenovirus: Adh1 5'-GCC GAG AAG GGC GTG CGC AGG TA-3'
Adh2 5'-ATG ACT TTT GAG GTG GAT CCC ATG GA-3'

Chlamydia pneumoniae: CpnA 5'-TGA CAA CTG TAG AAA TAC AGC-3'
CpnB 5'-CGC CTC TCT CCT ATA AAT-3'

Parainfluenzavirus type 1:
PIV1 1 5'-CAC ATC CTT GAG TGA TTA AGT TTG ATG A-3'
PIV1 2 5'-ATT TCT GGA GAT GTC CCG TAG GAG AAC-3'

Parainfluenzavirus type 3:
PIV3 1 5'-TAG CAG TAT TGA AGT TGG CA-3'
PIV3 2 5'-AGA GGT CAA TAC CAA CAA CTA-3'

Respiratory Syncytial Virus (RSV):
RSV1 5'-TGT TAT AGG CAT ATC ATT GA-3'
RSV 2 5'-TTA ACC AGC AAA GTG TTA GA-3'

are put in combination with one another after reverse transcription, where appropriate, of part of the patient's samples into a multiplex PCR, and

then hybridization solutions biotinylated at the 3′ end

Probes (3′ end biotinylated):

Sonden (3'-Ende biotinyliert):

Enterovirus: EV3 5'-GAA ACA CGG ACA CCC AAA GTA-3'

Mycoplasma pneumoniae: MP3 5'-ACT CCT ACG GGA GGC AGC AGT A-3'

Influenzavirus type A: InfA3 5'-GTC CTC ATC GGA GGA CTT GAA TGGAATGAT-3'

Influenzavirus type B: InfB3 5'-GTC AAG AGC ACC GAT TAT CAC C-3'

Adenovirus: Adh 3: 5'- CTC GAT GAC GCC GCG GTG C-3'

Chlamydia pneumoniae: CpnC 5'-TCT TGC TAC CTT CTG TAC TAA C-3'

Parainfluenzavirus type 1: PIV1C 5'-TAC CTT CAT TAT CAA TTG GTA AGT CAA TAT ATG -3'

Parainfluenzavirus type 3: PIV3C 5'-AAA ATT CCA AAA GAG ACC GGC -3'

RSV: RSV3 5'-TAC ACC TGC ATT AAC ACT AA-3'

are used as probes.